Russian Journal of Organic Chemistry, Vol. 39, No. 1, 2003, pp. 49–56. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 1, 2003, pp. 60–66.

Synthesis and Stereochemistry of Some 3-Azabicyclo[3.3.1]nonane Derivatives

G. F. Vafina, G. R. Yakhina, T. V. Khakimova, L. V. Spirikhin, F. Z. Galin, and M. S. Yunusov

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: chemorg@anrb.ru

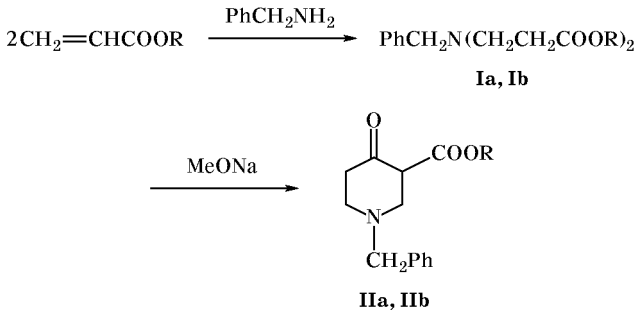
Received October 24, 2001

Abstract—Michael reactions of methyl (ethyl) 1-benzyl-4-oxopiperidine-3-carboxylates with a number of α,β-unsaturated carbonyl compounds result in formation of 6- and 6,8-substituted methyl (ethyl) 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylates. Stereochemical aspects of these reactions were studied, and some further transformations of the products were performed.

The ease of preparation of 3-azabicyclo[3.3.1]-nonanes (3-ABN) from accessible and cheap starting compounds, the unique reactivity of this bicyclic system, and wide spectrum of biological activity of 3-ABN derivatives make them convenient models for studying target-oriented transformations with the goal of obtaining new structures with desired properties.

We have studied Michael reaction of methyl and ethyl 1-benzyl-4-oxopiperidine-3-carboxylates **IIa** and **IIb** with various alkyl vinyl ketones and unsaturated aldehydes. A practical procedure for preparation of esters **IIa** and **IIb** is based on the reaction of methyl (or ethyl) acrylate with benzylamine, which gives 88–90% of amines **Ia** and **Ib**, and subsequent Dieckmann cyclization of the latter. The intramolecular condensation of **Ia** and **Ib** was effected by the action of sodium methoxide in benzene [1], and esters **IIa** and **IIb** were obtained in 56–93% yield (Scheme 1).

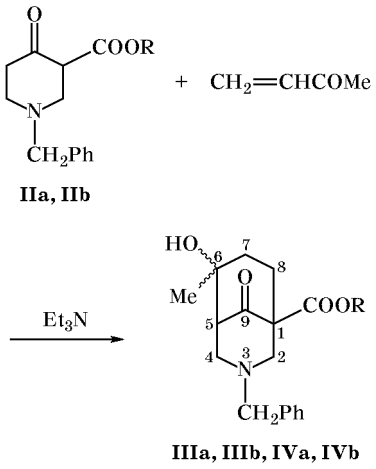
Scheme 1.



R = Me (**a**), Et (**b**).

The Michael reactions of methyl vinyl ketone with compounds **IIa** and **IIb** in methanol in the presence of 1.1 equiv of triethylamine [2] afforded 6-hydroxy-6-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylates **IIIa**/**IIIb** and **IVa**/**IVb** as mixtures of stereoisomers at a ratio of 1 : 8 and 1.5 : 8, respectively (yield 80–92%; Scheme 2).

Scheme 2.



IIa, **IIIa**, **IIIb**, R = Me; **IIb**, **IVa**, **IVb**, R = Et.

Compound **IIIa** was isolated as individual isomer in the crystalline state, and its stereochemical structure and intramolecular interactions were examined. In the one-dimensional *J*-modulation ^{13}C NMR spectrum of **IIIa**, the multiplicities of all signals were consistent

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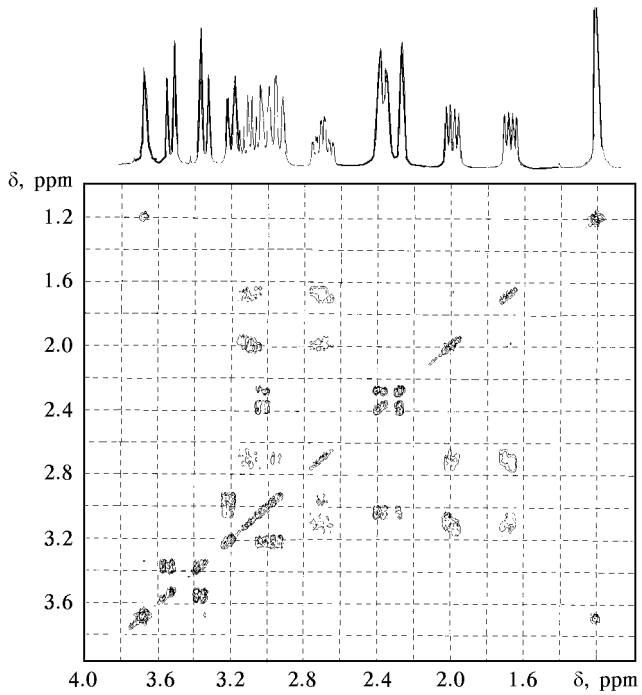
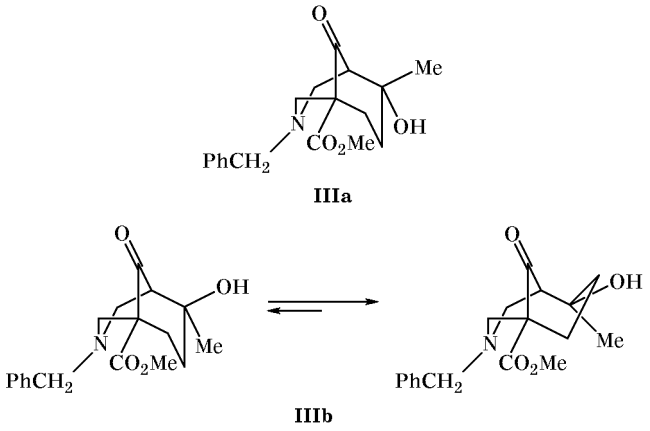


Fig. 1. Two-dimensional ^1H–^1H NMR correlation spectrum (COSY) of methyl 3-benzyl-6-hydroxy-6-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (**IIIa**).

with the assumed structure: 2 quartets, 5 triplets, 6 doublets, and 4 singlets were present. The ^1H and ^{13}C signals from the methyl group on C^6, carbonyl carbon atom (C^9), as well as from the ester carbon atoms and those of the benzyl group, can readily be assigned. The detailed assignment of the skeletal carbon atoms in structure **IIIa** was performed on the basis of the COSYHH45° and CHCORR spectra (Figs. 1, 2). The upfield region of the CHCORR spectrum (Fig. 2) contains two triplets with δ_C 31.87 and 34.67 ppm, to which two pairs of diastereotopic protons correspond. Taking into account β,γ-effects of the substituents, we can contend that the C^7 signal is located in a weaker field relative to the C^8 signal. The difference in the chemical shifts of protons on C^7 is relatively greater due to effect of the methyl and hydroxy groups in the β-position. Moreover, the downfield shift of the axial proton on C^7 in 3-azabicyclo[3.3.1]nonane derivatives is caused by the effect of lone electron pair on the nitrogen [4]. The *AB* quartet from geminal protons at the carbon atom with δ 61.85 ppm is typical of benzyl methylene group. The 5-H proton should be coupled with those attached to C^4, and the two-dimensional spectrum (Fig. 1) contains to cross peaks from 5-H. Then, the doublets of doublets at δ 2.40 and 3.04 ppm belong to protons on C^4 (δ_C 56.13 ppm), and the signal at δ_C 62.57 ppm corresponds to C^2. As might be expected, the coupling mode of protons on C^2 indicates that they are relatively distant from the other protons: they appear in the ^1H NMR spectrum as an *ABX* spin system with a geminal constant of –11.5 Hz and a long-range constant of 2.2 Hz. These data mean that the axial proton on C^2 is coupled with the axial proton on C^8. The equtorial proton on C^2 is characterized by a long-range coupling (^4J = 1.6 Hz) with the equatorial proton on C^4. The *W*-like arrangement of the above protons on C^2 and C^8 and on C^2 and C^4 suggests that conformational equilibrium is displaced toward the *chair–chair* conformer. Evidences in favor of this conformation are the long-range coupling constants $J_{2\text{-}ax,8\text{-}ax}$ and $J_{2\text{-}eq,8\text{-}eq}$, Bohlmann bands in the region 2600–2800 cm^{-1} of the IR spectrum of **IIIa** in KBr [3], and the results of AM1 calculations. The 6-hydroxy group in **IIIa** occupies equatorial position, and the methyl group is axial. In keeping with the calculated interatomic distances, Overhauser effect should be observed for 5-H and axial methyl protons. This was confirmed by the results of NOEDIFF experiments.

Scheme 3.



The NMR spectra of isomer **IIIb** are characterized by quite different chemical shifts of almost all protons and carbon nuclei. A different coupling system is observed in the ^1H NMR spectrum, so that we concluded that conformational equilibrium of compound **IIIb** is displaced toward the *chair–boat* conformer. There is no $J_{2\text{-}ax,8\text{-}ax}$ constant, but the long-range 2-H_{eq}–4-H_{eq} coupling ($J \approx 1.6$ Hz) in the piperidine ring is retained. The difference in the chemical shifts of protons on C^7 decreases (Δδ 0.42 ppm), for the effect of lone electron pair on the nitrogen is insignificant in the *chair–boat* conformation. The chemical shifts of protons on C^2 change to the reverse values,

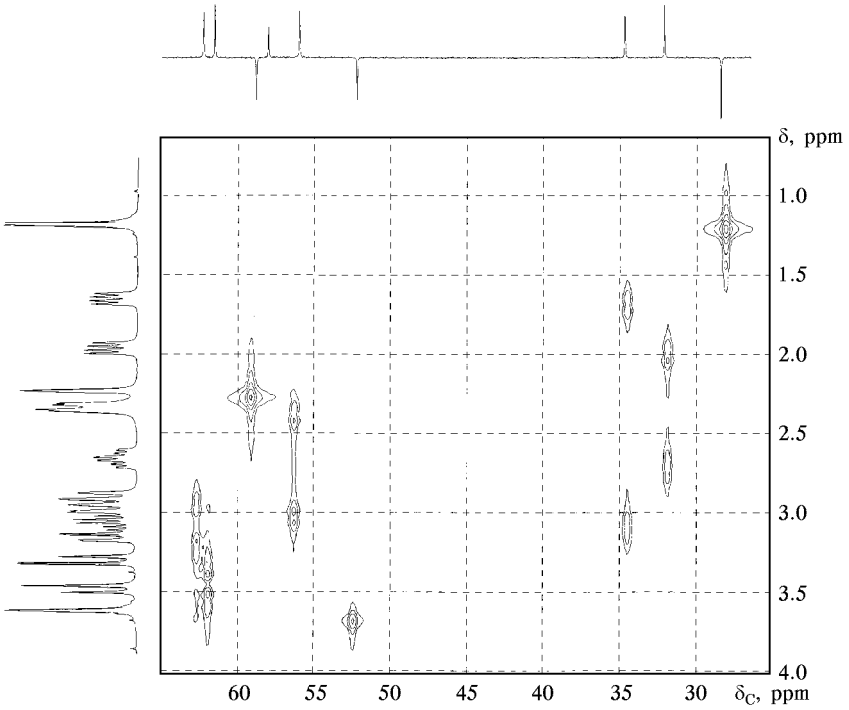


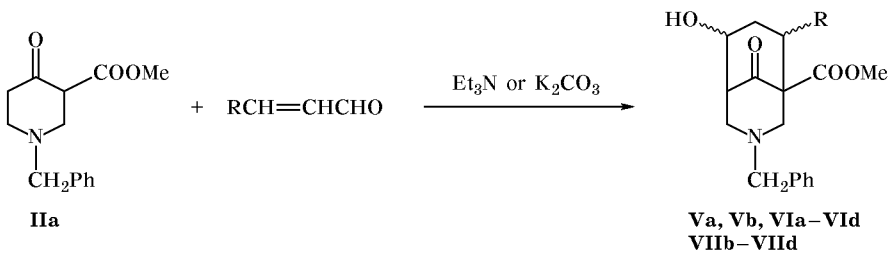
Fig. 2. Two-dimensional ^{1}H–^{13}C NMR correlation spectrum (CHCORR) of methyl 3-benzyl-6-hydroxy-6-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (**IIIa**).

presumably due to change of orientation of the methoxycarbonyl group in the β-position. The upfield shift of the carbonyl carbon signal (C^9) by 4 ppm in the ^{13}C NMR spectrum can be regarded as an indirect proof for the change of conformation [4]. The C^7 and C^8 signals are displaced downfield by ~6–7 ppm, and those from C^2 and C^4 shift upfield. Thus the hydroxy group tends to occupy equtorial position. We have revealed no appreciable displacement of conformational equilibria for compounds **IIIa** and **IIIb** by recording the ^{1}H NMR spectra at various temperatures (25–55°C).

By reaction of methyl 1-benzyl-4-oxopiperidine-3-carboxylate (**IIa**) with acrolein, crotonaldehyde, and cinnamaldehyde, we obtained in high yields 6- and 6,8-substituted 3-azabicyclononanes **Va**, **Vb**, **VIa**–**VId**, and **VIIb**–**VIId** (Scheme 4). The reactions were carried out by two procedures: (1) in methanol in the presence of triethylamine and (2) in acetone in the presence of potassium carbonate.

The product obtained from acrolein in methanol in the presence of Et_3N in quantitative yield was a mixture of epimers **Va** and **Vb** at a ratio of 4:1. When the reaction was performed in acetone in the presence of potassium carbonate, the ratio **Va**:**Vb** was 1:4. Thus the stereoselectivity of Michael addition of **IIa** to acrolein changes to the reverse on variation of the reaction conditions. The isomer ratio was determined from the 6-H signal intensity in the ^{1}H NMR spectrum. The structure of **Va** and **Vb** was confirmed by

Scheme 4.

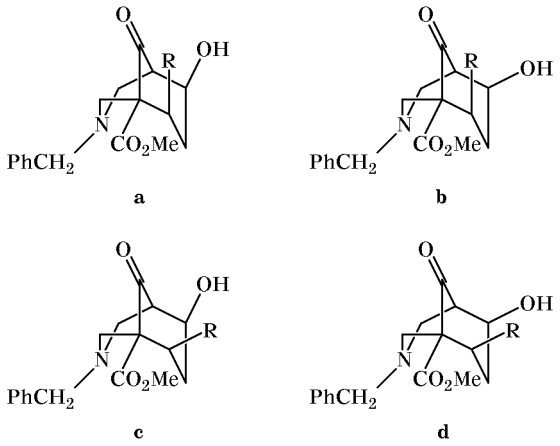


Va, **Vb**, R = H; **VIa**–**VId**, R = Me; **VIIb**–**VIId**, R = Ph.

the ^{1}H and ^{13}C NMR spectra (both one- and two-dimensional). The hydroxy group in isomer **Va** is equatorial, as follows from the position and multiplicity of the 6-H signal. The axial proton gives a more upfield signal than the equatorial one. The 6-H signal in the spectrum of **Va** is a doublet of triplets characterized by a large axial–axial coupling constant ($^3J_{6\text{-}ax,7\text{-}ax}$ = 13 Hz, $^3J_{6\text{-}ax,7\text{-}eq}$ = 5 Hz, $^3J_{6\text{-}ax,5}$ = 5 Hz); all coupling constants for the 6-H proton in isomer **Vb** fall into the range from 4 to 6 Hz ($W_{1/2}$ = 9 Hz).

The ^{1}H and ^{13}C NMR spectra of the reaction mixture obtained from piperidinone **IIa** and crotonaldehyde suggest the presence of four isomers of product **VI**. As with compound **VII**, the following stereoisomeric structures of azabicyclononane **VI** in the *chair–chair* conformation are possible: OH_{ax}, Me_{ax} (**a**); OH_{eq}, Me_{ax} (**b**); OH_{ax}, Me_{eq} (**c**); OH_{eq}, Me_{eq} (**d**) (Scheme 5).

Scheme 5.



VI, R = Me; **VII**, R = Ph.

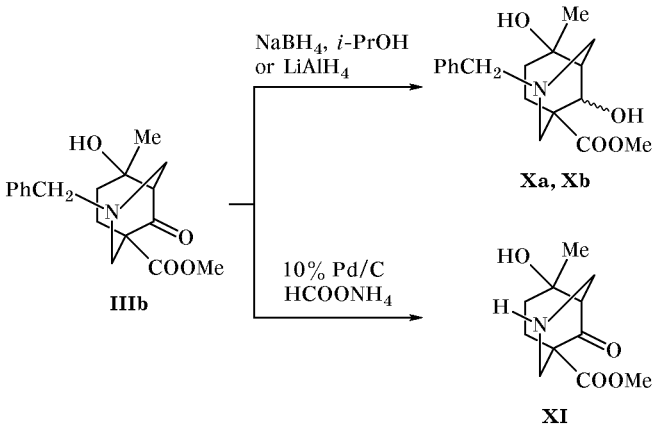
The most characteristic signals of isomers **VIa**–**VId** in both proton and carbon resonance spectra are those from the 6-hydroxy proton (δ 4.0–4.4 ppm) and C^6 (δ_C 72–76 ppm). According to the calculation results [5] and published data [6], the most upfield among these signals, δ_C 69.8 ppm, belongs to structure **VIa**, and the most downfield, δ_C 75.16 ppm,* to **VId**. Intermediate δ_C values, 70.53 and 74.57 ppm, correspond to isomers **VIb** and **VIc**, respectively. The ratio of isomers **VIa**–**VId** was determined from the intensities of doublet signals from the 8-CH_3 protons in the ^{1}H NMR spectrum. This ratio was found to depend on the reaction conditions. When triethylamine was used as a base, stereoisomer **VIb** prevails in the mixture (**a**:**b**:**c**:**d** = 3.6:5:1:1.2), while potassium carbonate as catalyst favors predominant formation of structure **VId** with equatorial orientation of the substituents on C^6 and C^8 (**a**:**b**:**c**:**d** = 1.8:0.5:3.5:4).

The reaction of compound **IIa** and cinnamaldehyde in the presence of triethylamine gave three isomers **VIIb**–**VIId** (according to the NMR data). As in the preceding case, the major isomer is **VIIb** (**b**:**c**:**d** = 7:2.3:1). Presumably, isomer **VIIa** is not formed for steric reasons. Isomer **VIId** having the phenyl and hydroxy groups in equatorial positions is formed in trace amounts. The same reaction performed in the presence of K_2CO_3 resulted in formation of two isomers **VIIc** and **VIId** at a ratio of 3:2.

Isomer mixtures **Va**/**Vb** and **VIa**–**VId** (obtained in the presence of triethylamine) were converted into the corresponding acetates **VIIIa**/**VIIIb** and **IXa**–**IXd**, following a standard procedure. Their yield was 85–88%, and the ratio was the same as for the initial alcohols.

We also tried to reduce the carbonyl group (C^9=O) in the prepared 3-ABN derivatives with sodium tetrahydridoborate. The reduction of **IIIb** was carried out in anhydrous methanol and 2-propanol. No reaction in methanol was observed. In 2-propanol, we obtained a mixture of epimeric alcohols **Xa** and **Xb** at a ratio of 3:2 (overall yield 60%). The reduction with $LiAlH_4$ afforded 35% of pure alcohol **Xb** (Scheme 6). Debenzylation of compound **IIIb** in methanol over Pd/C (10% of Pd) in the presence of ammonium formate [7] led to formation of product **XI** in 40% yield. The structure of **Xa**, **Xb**, and **XI** was established by comparing their ^{13}C NMR spectra with that of initial *N*-benzyl derivative **IIIb**.

Scheme 6.



* All signals in the ^{13}C NMR spectra of compounds **VId** and **VIId** are displaced upfield due to complex formation with triethylamine.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-III 300 instrument operating at 300.13 and 75.47 MHz, respectively; chloroform-*d* was used as solvent (10–20% solutions), and tetramethylsilane, as internal reference. The IR spectra were obtained on UR-20 and Specord M-80 spectrometers from samples prepared as thin films, Nujol mulls, KBr pellets, or solutions in chloroform. The mass spectra (70 eV) were run on an MKh-1306 spectrometer (ion source temperature 150–200°C). GLC analysis was performed on a Chrom-5 chromatograph equipped with a flame-ionization detector; 12-m column; stationary phase 5% of SE-30 on Inerton Super (0.12–0.16 mm); carrier gas flow rate 60 ml/min; oven temperature programming from 50 to 300°C.

The progress of reactions was monitored by TLC on Silufol UV-254 plates. Individual compounds were isolated by column chromatography on neutral Al_2O_3 using the following solvent systems: A: methylene chloride–methanol (100, 100:1, 50:1, 25:1, 10:1); B: benzene–ether–methanol (1:2, 2:1, 20:10:3); and C: benzene–methanol (100, 100:1, 50:1, 25:1, 10:1).

Bis(2-alkoxycarbonylethyl)benzylamines Ia and Ib. Freshly distilled benzylamine, 46 ml (1.0 mol), was added with stirring to 95 ml (2.1 mol) of freshly distilled methyl or ethyl acrylate in 100 ml of anhydrous methanol. The mixture was heated for 4.5 h under stirring, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography using eluent system A. Yield 113.85 g (80.7%).

Bis(2-methoxycarbonylethyl)benzylamine (Ia). ^{13}C NMR spectrum, δ_C, ppm: 32.39 t and 49.05 t (CH_2), 51.43 q (COO**Me**), 58.21 t (C**H**$_2$Ph), 127.19–128.22 d and 138.62 s (Ph), 172.73 s (COO). ^1H NMR spectrum: 2.80 t and 2.48 t (4H, CH_2), 3.55 q (2H, *AB* system C**H**$_2$Ph), 3.63 s (3H, COOMe), 7.20 s (H_{arom}).

Alkyl 1-benzyl-4-oxopiperidine-3-carboxylates IIa and IIb. Amine **Ia**, 10.3 g, was added dropwise under stirring to a suspension of 3.0 g of sodium methoxide in 15 ml of dry benzene. The mixture was stirred for 3.5 h under reflux, cooled to 10°C, and carefully poured into 28 ml of water. The mixture was stirred until the ketone sodium salt dissolved completely, the organic phase was separated, and the aqueous phase was neutralized with 3.1 ml of acetic acid and extracted with benzene (3 × 100 ml). The solvent was distilled off from the extract under reduced pressure, and the residue was purified by column chromatography on Al_2O_3.

Methyl 1-benzyl-4-oxopiperidine-3-carboxylate (IIa). Yield 93%. According to the GLC data, the product was a mixture of stereoisomers at a ratio of 97:3. Solvent system C was used as eluent for column chromatography. ^{13}C NMR spectrum, δ_C, ppm: 48.76 t (C^2), 49.95 t (C^6), 52.28 d (C^3), 55.61 t (C^5), 56.53 q (COO**Me**), 61.59 t (**C**H_2Ph), 126.46–128.30 d, 138.07 s (Ph), 170.48 s (CO, ester), 204.10 s (CO, ketone).

Ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (IIb). Yield 56%. ^1H NMR spectrum, δ, ppm: 1.25 t (Me), 2.60 t (2H, 2-H), 3.25 t (2H, 6-H), 3.50 m (1H, 3-H), 4.25 q (2H, CH_2), 7.35 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 14.34 q (Me), 48.56 t (C^2), 49.95 t (C^6), 51.40 d (C^3), 55.00 t (C^5), 61.59 t (**C**H_2CH$_3$), 62.21 t (**C**H_2Ph), 126.53–127.88 d, 138.12 s (Ph), 170.48 s (CO, ester), 204.04 s (CO, ketone). The product was purified via transformation into the corresponding hydrochloride.

Ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride. Compound **IIb**, 4.4 g, was dissolved in 12 ml of diethyl ether, and 3 ml of an alcoholic solution of HCl was added. The colorless precipitate was filtered off and repeatedly washed with ether. Yield 3.7 g, mp 155°C.

Methyl (ethyl) 9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylates (*general procedure***).** *a.* Freshly distilled triethylamine, 17.5 ml (0.11 mmol), and freshly distilled ketone or aldehyde, 0.15 mmol, were added in succession under stirring to a solution of 0.1 mmol of compound **IIa** or **IIb** in 40 ml of anhydrous methanol. The mixture was stirred for 24 h (6–8 h in the reaction with acrolein) at room temperature, the solvent was distilled off, and the residue was purified by column chromatography using solvent system B.

Methyl 3-benzyl-6-hydroxy-6-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (IIIa/IIIb). IR spectrum ($CHCl_3$), ν, cm^{-1}: 832, 848, 1535, 1704, 1736, 2508, 3600 (OH_{eq}), 3680 (OH_{ax}). Isomer ratio 1:8. Isomer **IIIa**: mp 118–121°C (from ether). ^1H NMR spectrum, δ, ppm: 1.22 s (3H, Me), 1.70 d.d (1H, 7-H_{eq}, ^2J = –13.6, $^3J_{7\text{-}eq,8\text{-}eq}$ = 6.3 Hz), 2.02 d.d (1H, 8-H_{eq}, ^2J = –13.6, $^3J_{8\text{-}eq,7\text{-}eq}$ = 6.3 Hz), 2.29 br.s (1H, 5-H), 2.40 d.d (1H, 4-H_{ax}, ^2J = –11.9, $^3J_{4\text{-}ax,5}$ = 3.2 Hz), 2.74 d.d.d.d (1H, 8-H_{ax}, J = –13.6, 13.5, 6.6, 2.2 Hz), 2.97 d.d (1H, 2-H_{eq}, ^2J = –11.5, $^4J_{2\text{-}eq,4\text{-}eq}$ = 1.6 Hz), 3.04 d.d.d (1H, 4-H_{eq}, ^2J = –11.9, $^3J_{4\text{-}eq,5}$ = 2.5, $^4J_{4\text{-}eq,2\text{-}eq}$ = 1.6 Hz), 3.05 d.d.d (1H, 7-H_{ax}, ^2J = –13.6, $^3J_{7\text{-}ax,8\text{-}ax}$ = 13.5, $^3J_{7\text{-}ax,8\text{-}eq}$ = 6.6 Hz), 3.24 d.d (1H, 2-H_{ax}, ^2J = –11.5, $^4J_{2\text{-}ax,8\text{-}ax}$ = 2.2 Hz), 3.40 and

3.60 d (2H, C**H**$_2$Ph, ^2J = –12.9 Hz), 3.72 s (3H, COO**Me**), 7.35 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 28.04 q (Me); 31.88 t (C^8); 34.67 t (C^7); 52.34 q (COO**Me**); 56.13 t (C^4); 58.24 s (C^1); 59.00 d (C^5); 61.85 t (**C**H$_2$Ph); 62.57 t (C^2); 78.69 s (C^6); 127.51 d, 128.75 d, 128.92 d, 137.99 s (Ph); 171.26 s (CO, ester), 210.36 s (CO, ketone).

Isomer **IIIb**: ^{1}H NMR spectrum, δ, ppm: 2.10 s (3H, Me), 2.22 m (1H, 2-H$_{ax}$, ^2J = –11.6 Hz), 2.32–2.41 m (2H, 8-H$_{eq}$, 5-H), 2.46 m (1H, 7-H$_{eq}$, ^2J = –10.6 Hz), 2.47 m (1H, 4-H$_{ax}$, ^2J = –10.8 Hz), 2.65 d.d.d (1H, 8-H$_{ax}$, ^2J = –10.4, $^3J_{8\text{-}ax,7\text{-}ax}$ = 10.3, $^3J_{8\text{-}ax,7\text{-}eq}$ = 5.1 Hz), 2.88 m (1H, 7-H$_{ax}$), 3.01 m (1H, 4-H$_{eq}$), 3.34 d.d (1H, 2-H$_{eq}$, ^2J = –11.6, $^4J_{2\text{-}eq,4\text{-}eq}$ = 1.6 Hz), 3.55 d and 3.62 d (2H, C**H**$_2$Ph, ^2J = –12.8 Hz), 3.73 s (3H, COO**Me**), 7.30 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 29.92 q (Me); 38.84 t (C^8); 40.47 t (C^7); 52.32 q (COO**Me**); 53.66 t (C^4); 58.92 d (C^5); 60.40 s (C^2); 61.21 t (C**H**$_2$Ph); 61.71 t (C^1); 75.55 s (C^6); 127.45 d, 128.69 d, 128.85 d, 137.78 s (Ph); 172.07 s (CO, ester), 206.37 s (CO, ketone).

Ethyl 3-benzyl-6-hydroxy-6-methyl-9-oxo-3-azabicyclo[3.3.1]nonan-1-carboxylate (IVa/IVb). Yield 78%. Isomer ratio 1.5:8. Isomer **IVb**: ^{1}H NMR spectrum, δ, ppm: 1.17 t (3H, CH$_2$C**H**$_3$), 2.04 s (3H, 6-Me), 4.13 q (2H, C**H**$_2$CH$_3$), 7.22 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 13.94 q (CH$_2$**Me**); 25.56 q (Me); 29.66 t (C^8); 38.60 t (C^7); 40.32 t (C^4); 52.06 s (C^1); 53.44 d (C^5); 60.22 t (**C**H$_2$Ph); 60.95 t (**C**H$_2$Me); 61.21 t (C^2); 61.57 s (C^6); 127.21, 128.46, 128.68 d, 137.69 s (Ph); 171.35 s (CO, ester), 207.13 s (CO, ketone).

b. Potassium carbonate, 1.5 mmol, was added under argon to a solution of 1 mmol of compound **IIa** in 10 ml of anhydrous acetone, and the mixture was stirred for 15 min at room temperature. A solution of 1.5 mmol of acrolein in 2 ml of anhydrous acetone was slowly added in a dropwise manner. The mixture was stirred for 7 h, the precipitate was filtered off, and the solvent was removed from the filtrate under reduced pressure. Yield of **Va**/**Vb** 99.9%.

Methyl 3-benzyl-6-hydroxy-9-oxo-3-azabicyclo-[3.3.1]nonane-1-carboxylate (Va/Vb). IR spectrum, ν, cm^{-1}: 744, 948, 1028, 1044, 1076, 1088, 1108, 1268, 1356, 1456, 1688, 1720, 1728, 1744, 3448. Isomer **Va**: ^{1}H NMR spectrum, δ, ppm: 1.90–2.11 m (1H, 7-H$_{eq}$), 2.18 d.d.d (1H, 8-H$_{eq}$, ^2J = –13.1, $^3J_{8\text{-}eq,7\text{-}ax}$ = 6.7, $^3J_{8\text{-}eq,7\text{-}eq}$ = 2.2 Hz), 2.27 d.d.d.d (1H, 8-H$_{ax}$, ^2J = –13.1, $^3J_{8\text{-}ax,7\text{-}ax}$ = 13.0, $^3J_{8\text{-}ax,7\text{-}eq}$ = 6.0, $^4J_{8\text{-}ax,2\text{-}ax}$ = 2.2 Hz), 2.46 d.d (1H, 4-H$_{ax}$, ^2J = –12.1, $^3J_{4\text{-}ax,5}$ = 4.1 Hz), 2.61 m (1H, 5-H), 2.91 d.d (1H, 2-H$_{eq}$, ^2J = –10.6, $^4J_{2\text{-}eq,4\text{-}eq}$ = 1.6 Hz), 2.99 d.d.d (1H, 7-H$_{ax}$, ^2J = –13.0 Hz, $^3J_{7\text{-}ax,8\text{-}ax}$ = 13.0, $^3J_{7\text{-}ax,8\text{-}eq}$ = 6.7 Hz), 3.10 d.d (1H, 2-H$_{ax}$, ^2J = –12.0, $^4J_{2\text{-}ax,8\text{-}ax}$ = 2.2 Hz), 3.35 d and 3.58 d (2H, C**H**$_2$Ph, ^2J = –13.0 Hz), 3.50 d.d (1H, 4-H$_{eq}$, ^2J = 12.1, $^4J_{4\text{-}eq,2\text{-}eq}$ = 1.6 Hz), 3.68 s (3H, COO**Me**), 4.10 d.t (1H, 6-H$_{ax}$, $^3J_{6\text{-}ax,7\text{-}ax}$ = 13.0, $^3J_{6\text{-}ax,7\text{-}eq}$ = 5.0, $^3J_{6\text{-}ax,5}$ = 5.0 Hz), 7.35 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 30.05 t (C^7); 30.38 t (C^8); 52.28 q (COO**Me**); 54.13 t (C^4); 54.42 d (C^5); 58.17 s (C^1); 61.15 t (C^2); 61.76 t (**C**H$_2$Ph); 72.30 d (C^6); 127.43 d, 128.20 d, 128.54 d, 137.83 s (Ph); 171.06 s (CO, ester); 209.23 s (CO, ketone).

Isomer **Vb**. ^{13}C NMR spectrum, δ_C, ppm: 26.14 t (C^7); 31.70 t (C^8); 54.86 q (COO**Me**); 54.86 d (C^5); 56.56 s (C^1); 58.74 t (C^4); 61.70 t (C^2); 61.87 t (**C**H$_2$Ph); 76.28 d (C^6); 127.37 s, 128.45 s, 128.92 s, 137.93 s (Ph); 171.09 s (CO, ester); 210.01 s (CO, ketone).

Methyl 3-benzyl-6-hydroxy-8-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (VIa–VId) was synthesized follwing the general procedure, method *a*. Yield 96% (95% according to *b*). Isomer ratio **a**:**b**:**c**:**d** = 3.6:5:1:1.2. IR spectrum, ν, cm^{-1}: 680, 692, 1080, 1728, 1736, 3432 (film); 3688, 3696 (CHCl$_3$). *m*/*z* 317 [*M*]$^+$. $C_{18}H_{23}O_4N$. Major isomer **VIb**: ^{1}H NMR spectrum, δ, ppm: 0.83 d (3H, Me, *J* = 6.6 Hz), 3.70 s (3H, COO**Me**), 4.00 m (1H, 6-H), 7.30 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 16.22 q (Me); 34.15 d (C^8); 38.47 t (C^7); 52.03 q (COO**Me**); 53.6 d (C^5); 54.00 s (C^1); 54.08 t (C^4); 62.08 t (C^2); 62.36 t (**C**H$_2$Ph); 70.44 d (C^6); 126.94–128.81 d, 137.96 s (Ph), 170.92 s (CO, ester); 209.57 s (CO, ketone). Isomer mixture **VIa**–**VId** was converted into the corresponding hydrochloride (see above), mp 176–178°C.

Isomer **VIa**. ^{1}H NMR spectrum, δ, ppm: 0.95 d (Me, *J* = 6.42 Hz), 3.60 s (3H, COO**Me**), 4.20 m (1H, 6-H). ^{13}C NMR spectrum, δ_C, ppm: 18.67 q (Me); 36.20 d (C^8); 41.13 t (C^7); 51.80 q (COO**Me**); 55.92 d (C^5); 55.97 s (C^1); 58.70 (C^2); 62.11 t (**C**H$_2$Ph); 63.63 t (C^4); 69.84 d (C^6); 127.33–128.72 d, 137.56 s (Ph); 170.82 s (CO, ester); 206.43 s (CO, ketone).

Isomer **VIc**. ^{1}H NMR spectrum, δ, ppm: 1.05 d (Me, *J* = 7.14 Hz), 3.65 s (3H, COO**Me**), 4.27 br.s (1H, 6-H). ^{13}C NMR spectrum, δ_C, ppm: 16.48 q (Me); 35.11 d (C^8); 37.40 t (C^7); 51.41 q (COO**Me**); 56.73 s (C^1); 58.16 t (C^2); 61.18 t (C^4); 61.98 t

(**C**H_2Ph); 74.57 d (C^6); 127.39–128.75 d, 137.76 s (Ph); 172.87 s (CO, ester); 209.30 s (CO, ketone).

Isomer **VId**. ^{1}H NMR spectrum, δ, ppm: 0.90 d (3H, Me, J = 6.18 Hz), 3.73 s (3H, CO_2Me), 4.48 br.s (1H, 6-H). ^{13}C NMR spectrum,* δ_C, ppm: 19.38 (19.16) q (Me); 36.91 (29.04) d (C^8); 38.86 (40.69) t (C^7); 51.50 (52.03) q (COO**Me**); 54.09 d (C^5); 56.50 s (C^1); 58.28 t (C^4); 61.90 t (**C**H_2Ph); 62.85 t (C^2); 75.16 d (72.08) (C^6); 127.39–128.75 d, 137.87 s (Ph); 170.79 s (CO, ester); 207.50 s (CO, ketone).

Methyl 3-benzyl-6-hydroxy-9-oxo-8-phenyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (VIIb–VIId) was synthesized following the general procedure, method *a*. Yield 75%. Isomer ratio **b**:**c**:**d** = 7:2.3:1. *m*/*z* 379 $[M]^+$. $C_{23}H_{25}O_4N$. Major isomer **VIIb**: ^{13}C NMR spectrum, δ, ppm: 37.18 t (C^7); 45.16 d (C^8); 51.48 q (COO**Me**); 54.33 d (C^5); 54.60 s (C^1); 57.35 t (C^4); 62.25 t (**C**H_2Ph); 62.77 t (C^2); 70.28 d (C^6); 126.14–131.39 d, 136.58–137.54 s (Ph); 172.91 s (CO, ester); 208.55 s (CO, ketone).

Isomer **VIIc**. ^{13}C NMR spectrum, δ_C, ppm: 35.99 t (C^8); 45.93 d (C^7); 51.90 q (COO**Me**); 54.22 d (C^5); 58.15 t (C^4); 62.20 t (**C**H_2Ph); 63.35 t (C^2); 73.97 d (C^6); 126.93–131.23 d, 133.97–134.67 s (Ph); 169.79 s (CO, ester); 209.44 s (CO, ketone).

Isomer **VIId**. ^{13}C NMR spectrum, δ_C, ppm: 38.63 t (C^8); 44.99 d (C^7); 51.78 q (COO**Me**); 57.92 t (C^4); 61.43 t (**C**H_2Ph); 62.98 t (C^2); 72.15 t (C^6); 126.55–131.83 d, 134.89 s, 145.03 s (Ph); 170.57 s (CO, ester); 210.33 s (CO, ketone).

Methyl 3-benzyl-6-hydroxy-9-oxo-8-phenyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (**VIIb**–**VIId**) hydrochloride, mp 134–137°C.

Methyl 6-Acetoxy-3-benzyl-9-oxo-3-azabicyclo-[3.3.1]nonan-9-one (VIIIa/VIIIb) was synthesized by a standard procedure from isomer mixture **Va**/**Vb** (obtained by method *a*). Yield 85%. The isomer ratio remained unchanged. Major isomer **VIIIa**: ^{13}C NMR spectrum, δ_C, ppm: 20.92 q (**Me**CO); 26.58 d (C^8); 30.10 t (C^7); 51.45 q (COO**Me**); 52.31 d (C^5); 54.45 s (C^1); 58.09 t (C^4); 58.18 t (C^2); 61.53 t (**C**H_2Ph); 73.23 d (C^6); 127.45–128.94 d, 136.35 s (Ph); 169.61 s (CO, acetate); 170.54 s (CO, ester); 207.13 s (CO, ketone).

Isomer **VIIIb**. ^{13}C NMR spectrum, δ_C, ppm: 22.50 q (**Me**CO); 27.00 d (C^8); 51.27 q (COO**Me**); 52.36 d (C^5); 61.65 t (**C**H_2Ph); 78.00 d (C^6); 127.89–128.97 d, 138.95 s (Ph); 170.11 s (CO, acetate); 171.20 s (CO, ester); 208.53 s (CO, ketone).

Methyl 6-acetoxy-3-benzyl-8-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (IXa–IXd) was synthesized by a standard procedure from isomer mixture **VIa**–**VId** (obtained according to method *a*). Yield 88%. Major isomer **IXb**: ^{13}C NMR spectrum, δ_C, ppm: 16.37 q (Me); 21.12 q (**Me**CO); 33.95 d (C^8); 35.01 t (C^7); 50.85 d (C^5); 52.40 q (COO**Me**); 54.83 (C^2); 56.45 t (C^4); 61.86 s (C^1); 62.40 t (**C**H_2Ph); 71.87 d (C^6); 126.68–128.45 d, 137.84 s (Ph); 169.93 s (CO, acetate); 175.97 s (CO, ester); 207.80 s (CO, ketone).

Isomer **IXa**. ^{13}C NMR spectrum, δ_C, ppm: 18.64 q (Me); 21.21 q (**Me**CO); 34.56 t (C^7); 36.49 d (C^8); 50.67 d (C^5); 52.14 q (COO**Me**); 52.87 t (C^2); 53.79 t (C^4); 61.48 s (C^1); 62.08 t (**C**H_2Ph); 77.30 d (C^6); 126.45–128.64 d, 137.59 s (Ph); 169.76 s (CO, acetate), 170.13 s (CO, ester); 205.17 s (CO, ketone).

Methyl 6-acetoxy-3-benzyl-8-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (**IXa**–**IXd**) hydrochloride, mp 174–176°C.

Methyl 3-benzyl-6,9-dihydroxy-6-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylate (Xa/Xb). *a*. Compound **IIIb**, 0.5 g, was dissolved in 25 g of anhydrous isopropyl alcohol, and 0.2 g of $NaBH_4$ was added with stirring under a stream of argon. The mixture was heated for 6 h under reflux, a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with methylene chloride. After appropriate treatment, the residue was subjected to column chromatography using solvent system C as eluent. Yield 60%. According to the GLC data, the ratio of epimeric alcohols **Xa** and **Xb** was 6:4.

b. Lithium aluminum hydride, 0.06 g, was added with stirring to 0.5 g of compound **IIIb** in 10 ml of anhydrous THF. The mixture spontaneously warmed up to 30°C. It was heated for 6 h and treated as described above in *a*. Yield of **Xb** 35%. $C_{18}H_{24}NO_4$. *m*/*z* 319 $[M]^+$. Isomer **Xa**: ^{13}C NMR spectrum, δ_C, ppm: 26.50 t (C^8); 31.13 q (Me); 36.98 t (C^7); 45.24 d (C^5); 46.40 s (C^1); 52.33 q (COO**Me**); 54.52 t (C^2); 59.94 t (C^4); 62.46 t (**C**H_2Ph); 71.29 s (C^6); 74.70 d (C^9); 127.21–128.80 d, 138.07 s (Ph); 176.89 s (CO).

Alcohol **Xb**. ^{13}C NMR spectrum, δ_C, ppm: 23.31 q (Me); 44.32 t (C^8); 48.91 t (C^7); 51.81 q (COO**Me**); 52.26 t (C^2); 52.87 s (C^1); 59.87 d (C^5); 62.66 t (**C**H_2Ph); 68.44 s (C^6); 72.80 d (C^9); 127.67–128.58 d, 138.07 s (Ph); 176.89 s (CO).

* In parentheses are given the ^{13}C chemical shifts from the spectrum of the reaction mixture obtained according to method *a*.

Methyl 6-hydroxy-6-methyl-9-oxo-3-azabicyclo-[3.3.1]nonane-1-carboxylate (XI) was synthesized by the procedure described in [7]. Anhydrous ammonium formate, 15 mmol, was added in one portion to a suspension of 3 mmol of compound **IIIb** and an equal (by weight) amount of 10% Pd/C in 20 ml of anhydrous methanol, stirred in a stream of argon. The mixture was stirred for 45 min at the boiling point, the catalyst was filtered off and washed with chloroform, and the filtrate was combined with the washings and evaporated. Yield 40%. ^{13}C NMR spectrum, δ_C, ppm: 29.85 q (Me); 32.13 t (C^8); 33.29 t (C^7); 51.86 q (COO**Me**); 52.01 t (C^4); 60.26 s (C^1); 60.41 t (C^2); 74.62 s (C^6); 170.19 s (CO, ester), 206.93 s (CO, ketone).

This study was financially supported by the Ministry of Industry and Science of the Russian Federation (State Contract no. 41.002.1.1.1401).

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